EOSINOPHILIC MUCUS CHRONIC RHINOSINUSITIS:

AN IMMUNOLOGICAL PERSPECTIVE

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PRÉCIS

Immunoglobulin E (IgE) – mediated systemic fungal allergy and fungi in sinus eosinophilic mucus are considered pathologically important in patients with eosinophilic mucus chronic rhinosinusitis (EMCRS). They are used to subgroup these patients into the following: allergic fungal sinusitis (AFS), AFS-like, non-allergic fungal eosinophilic sinusitis (NAFES) and non-allergic, non-fungal eosinophilic sinusitis (NANFES). The relevance of this classification system was examined in this thesis according to the clinical characteristics, systemic immune responses and the sinonasal lymphocyte populations in EMCRS patients. In doing so, it was established that the EMCRS subgroups were not significantly different from one another. However, as a single group, EMCRS patients had a more severe form of sinus disease than patients with chronic rhinosinusitis without eosinophilic mucus (CRS).

The total IgE and fungal-specific IgE-mediated allergic parameters were not significantly different between allergic EMCRS patients and disease-control group, allergic rhinitis with fungal allergy (ARFA). This indicated that fungal allergy was not of central pathogenic importance in EMCRS. Regardless of fungal allergy or of the detection of fungi, EMCRS patients had an elevated humoral and cellular immune response to *Alternaria alternata* and *Aspergillus fumigatus* compared with healthy volunteers. EMCRS patients were distinguished from ARFA and CRS groups by elevated fungal-specific serum IgG3 levels. Fungal-specific peripheral blood mononuclear cell proliferation was also increased in EMCRS patients. While $CD4^+$ and $CD8^+$ T lymphocytes proliferated in a proportion of ARFA and CRS patients, $CD8^+$ T lymphocytes did not proliferate in EMCRS. This implied a dysregulated $CD8^+$ T cell response to fungi. Compared with CRS, polyps from EMCRS patients had a greater proportion of effector memory $CD8^+$ T lymphocytes lacking the cytotoxic phenotype defined by intracellular perforin. These findings indicated that

immunological mechanisms other than IgE-mediated fungal allergy were involved in EMCRS. These mechanisms were characterised by terminally differentiated and antigen-experienced $CD8^+$ T lymphocytes in the mucosa.

The work presented here showed that eosinophilic mucus represented a distinct clinico-pathological subset of chronic rhinosinusitis patients. The clinical subgrouping of EMCRS was unfounded as IgE-mediated allergy was not the principal pathogenic mechanism, and all the EMCRS subgroups had an elevated fungal-specific immune response. Although the nature of the fungal involvement and disease mechanisms remain to be determined, this thesis represents a major conceptual advance to determine the pathogenic processes in eosinophilic mucus chronic rhinosinusitis.